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1 *TITLE PAGE*

2 Title: Saccadic adaptation boosts ongoing gamma activity in a subsequent visuo-attentional task.

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ABSTRACT

Attention and saccadic adaptation (SA) are critical components of visual perception, the former enhancing sensory processing of selected objects, the latter maintaining the eye movements accuracy toward them. Recent studies propelled the hypothesis of a tight functional coupling between these mechanisms (Habchi et al., 2015; Gerardin et al., 2015), possibly due to shared neural substrates (Gerardin et al. 2012; Corbetta et al. 2008). Here, we used magnetoencephalography to investigate for the first time the neurophysiological bases of this coupling and of SA *per se*.

We compared visual discrimination performance of 12 healthy subjects before and after SA. Eye movements and magnetic signals were recorded continuously. Analyses focused on gamma band activity (GBA) during the pre-target period of the discrimination and the saccadic tasks.

We found that GBA increases after SA. This increase was found in the right hemisphere for both post-adaptation saccadic and discrimination tasks. For the latter, GBA also increased in the left hemisphere.

We conclude that oculomotor plasticity involves GBA modulation within an extended neural network which persists after saccadic adaptation, suggesting a possible role of gamma oscillations in the coupling between SA and attention.

KEYWORDS

Gamma oscillations, Magnetoencephalography, Oculomotor plasticity, Visuo-spatial attention

Humans make up to 200,000 saccadic eye movements daily. Saccades are categorized as either reactive saccades (RS) triggered by a sudden stimulus appearance, or intentionally driven voluntary saccades (VS) (Gaymard et al. 1998). Decreased performance of saccades can impair vision (Leigh and Zee 1999). Fortunately, brain-plasticity processes known as saccadic adaptation (SA) help preserve saccade accuracy by modulating oculomotor commands when neuro-muscular efficacy is durably altered due to growth, aging, fatigue or pathological conditions (Pélisson et al. 2010).

Thanks to the double-step paradigm (McLaughlin 1967) and to modern eye-tracking techniques, SA has become a convenient tool to explore sensorimotor plasticity *per se*. The underlying neural processes of SA were initially thought to be restricted to the cerebellum (Desmurget et al. 1998; Prsa and Thier 2011; Panouillères et al., 2015) but are nowadays known to comprise various cortical areas (Gerardin et al. 2012; Blurton et al. 2012).

Noteworthy, beyond an indirect effect of SA on visual perception related to plastic motoric changes, SA may also directly impact vision through modulation of visuo-spatial attention. Visual attention is a cognitive process that enhances the processing of visual signals arising from the attended part ('attentional focus') of our environment with respect to unattended locations (Posner 1980; Carrasco et al. 2000). The moment-to-moment position of this focus is determined by interaction of two main orienting components: the exogenous process, directing attention towards suddenly appearing stimuli, and the endogenous process which directs attention towards intentionally-driven goals. This dichotomy between exogenous and endogenous attention echoes the one between RS and VS. The similarities between attentional and saccadic systems are such that saccades are often qualified as 'overt shifts of attention' and that, in the framework of the premotor theory of attention, 'covert shifts of attention' are considered equivalent to inhibited saccades (Rizzolatti et al. 1987). Although the generality of the premotor theory of attention has

been criticized, its validity remains largely unaffected for exogenous attention (and corresponding reactive saccades) (Smith and Schenk 2012). Consistent with the premotor theory of attention, neural systems controlling attention and saccades strongly overlap (Corbetta 1998). Interestingly, this overlap has also been suggested by recent studies of the cortical substrates of SA: on the one hand adaptation of VS recruits areas of the Intra-Parietal Sulcus (IPS) whereas adaptation of RS activates the right Temporo-Parietal-Junction (rTPJ) (Gerardin et al. 2012; Panouillères et al., 2014), on the other hand IPS and rTPJ belong to the dorsal and ventral networks subtending, respectively, endogenous and exogenous attention (Corbetta et al., 2008).

Consistent with these overlapping neural substrates, a coupling between RS adaptation and exogenous attention has been proposed by the following behavioral studies. First, McFadden et al. (2002) claimed they managed to ‘adapt the shift of attention focus’ during a covert attentional task and found that the amplitude of RS elicited just after this ‘adaptation’ was similarly modified. Second, Gerardin and colleagues (2015) reported that increasing the attention load deployed during the RS adaptation exposure positively affected the amount of adaptation. Thus, these two studies suggested that experimental manipulations of the covert attention system impacts RS adaptation. Conversely, Khan et al. (2010) investigated the effect of SA on the exogenous displacement of the attentional focus which is coupled to saccades, and proposed that such pre-saccadic shift of attention changes after SA so as to remain spatially linked to the saccadic motor vector (see also Doré-Mazars and Collins 2005). Finally, Habchi et al. (2015) disclosed an effect of adaptation of leftward RS onto covert exogenous attention, by showing after adaptation a specific increase of the processing speed of unpredictable visual stimuli in detection and spatial discrimination tasks performed without eye movement. Interestingly, this boosting effect was found not only for the target location of the adapted saccade but also for more eccentric or less eccentric targets in the

adapted left hemifield. This spatial transfer can be related to the well-known fact that saccadic adaptation is not strictly spatially-selective, as adaptation of a single saccade affects all saccades landing within an extended zone around the adapted saccade landing position, known as the adaptive field (Straube et al. 1997; Frens and Van Opstal 1997).

Here, using MagnetoEncephaloGraphy (MEG), we aim at determining for the first time the neural underpinnings of SA as a candidate substrate of the coupling between oculomotor plasticity and exogenous attention. We investigated Gamma power, which reflects the amplitude of the fast cortical activity (35 Hz and above) elicited by the coordinated activity of large assemblies of neurons. Given that gamma band activity (GBA) is known to predict the sensory processing efficiency (Fries et al. 2001; Jensen et al. 2007; Tallon-Baudry and Bertrand, 1999) and to encode saccadic goals (Medendorp et al. 2007; Van Der Werf et al. 2008), we focused on pre-target GBA measured during the SA task as well as during a covert attention task performed pre- and post-adaptation.

1. MATERIALS & METHODS

1.1. Subjects

The experiment adheres to the code of ethics of the World Medical Association – Declaration of Helsinki (2008) and, in agreement with French law (March 4, 2002), received the approval of the Committee for Person Protection (CPP SUD EST IV, Lyon, France, A01180-39). 15 subjects were recorded and paid 60 euros for their participation. Among these 15, 12 subjects (7 females) were finally analyzed. The 3 subjects were discarded because of poor recording quality of the eye tracker (2 subjects) or because of high muscular activity (1 subject). The mean age of the 12 analyzed

subjects was $28.3 \text{ years} \pm 2.32 \text{ SD}$ (Standard Deviation). Subjects were all right-handed and with a normal or corrected-to-normal vision. All subjects were free from neurological or psychiatric disorders history; cognitive disorders preventing the comprehension of the instructions; consumption of psychotropic drugs, substances, or alcohol during the last 24 hours; participation to other experiments involving sensorimotor adaptation during the preceding week. After written consents obtained, each subject was assigned pseudo-randomly to one of the two sub-groups, corresponding to the possible orders of testing of the two experimental sessions (within-subject design, see General Design section).

1.2. Stimuli and procedure

1.2.1. General design

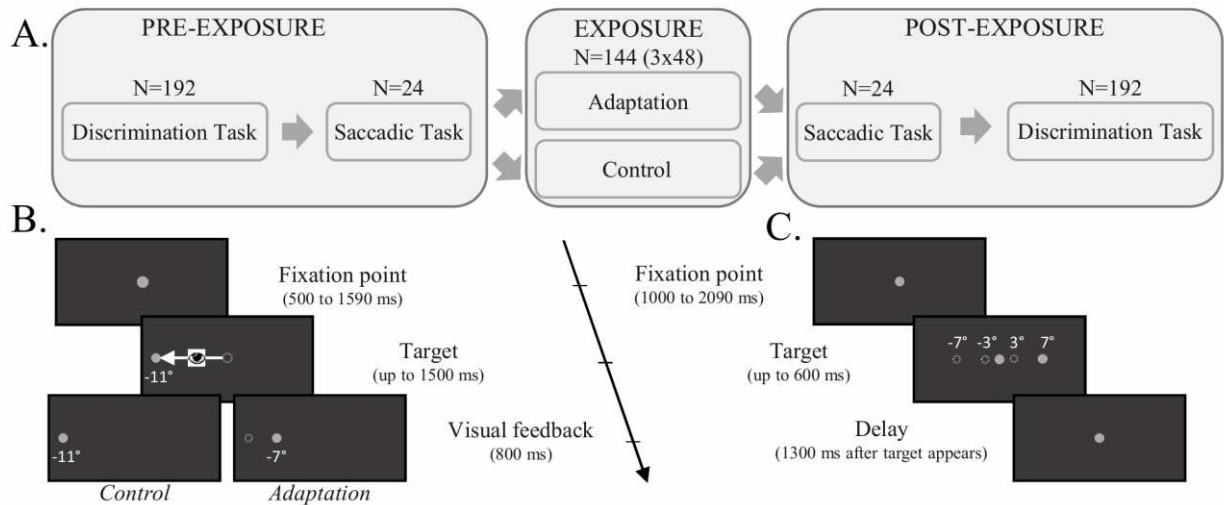


Figure 1: **A. Study general design.** Each subject underwent 2 experimental sessions, differing only by the Exposure phase (either Adaptation or Control). N = number of trials. **B. Time-line of a trial in the exposure task.** Note that in the pre- and post-exposure tasks (not shown), visual feedback is suppressed (visual scene is turned off) as soon as the saccade is detected. **C. Time-line of a trial in the discrimination task.** The dotted points represent the potential target position (red in the experiment), only one is turned on in each trial (at 7° in this example).

The experiment was carried out in the dimly lit shielded room of the MEG set-up (see section 1.4). Each subject was installed in a comfortable position with the head stabilized, facing a black wood panel containing a set of red LEDs of 0.25° of visual angle at 114 cm from subject's eyes, the measured contrast was 100%. Visual stimulation (LEDs ON or OFF) was controlled by a laboratory-made software running on a PC (windows XP) located outside of the shielded room. Monocular eye movements (right eye) were recorded at a 1000 Hz frequency using the EyeLink 1000 infrared tracker (SR research, Canada).

Subjects were submitted to two experimental sessions, each of which comprising identical pre-exposure and post-exposure phases as well as a specific exposure phase (Fig. 1A). In the 'adaptation' session, the exposure phase consisted in adaptation of leftward reactive saccades whereas in the 'control' session, un-adapted leftward reactive saccades were performed instead. In each session, the effects of exposure on saccade and on attention were measured by comparing between the pre- and post-exposure phases subjects' performance in a test saccade task and in a visual discrimination task, respectively. Contrasting these data between the two sessions provided specific effects of unilateral SA induced in the adaptation session. The delay between the two sessions was at least 14 days in order to avoid any retention of SA between sessions, based on a previous study disclosing that the retention of adaptation observed 5 days after exposure was no longer significant 11 days after (Alahyane and Pélisson 2005).

1.2.2. *Saccadic Tasks*

The saccadic adaptation task, also referred to as the adaptation exposure task, implemented the double-step paradigm introduced by (McLaughlin 1967). This paradigm consists in displacing the visual target while the subject is executing a saccade towards this peripheral target. Thanks to the saccadic suppression phenomenon, this intra-saccadic visual displacement is usually not consciously perceived by subjects and leads to a mismatch between post-saccadic eye fixation and target location which is interpreted by the central nervous system as a saccade aiming error. This procedure yields a progressive, exponential-like, change of saccade gain reaching an asymptote after around 100 trials in humans (see for review: Hopp and Fuchs 2004; Pélisson et al., 2010), thus, we chose a total number of 144 adaptation trials to optimize the steady state level of adaptation and the level of after effect .

Sequence of events in an adapted exposure trial (Fig. 1B). Subjects had first to fixate a central LED. After a delay of 500 to 1590 ms (uniformly randomized) a peripheral LED was flashed along the horizontal meridian at an eccentricity of 11° of visual angle to the left (-11°) of fixation and simultaneously, the central LED was turned off. The subject had to make a saccade towards the peripheral target (maximum allocated time: 1500 ms). When the saccade was detected (online eye velocity threshold: $80^\circ/\text{s}$), the visual target was shifted 4° inwards, namely a LED at -7° of visual eccentricity was turned on while the LED at -11° was turned off. This new visual target remained visible for 800 ms after the detection of the saccade to provide visual feedback about the target location and allow corrective saccades. The subject then had a delay of 2000 ms to blink and look back to the central fixation dot before the next trial started.

The saccadic control task, also referred to as the control exposure task, was identical to the adaptation task except that there was no jump of the visual target in any of the trials, the -11° LED staying on for 800 ms after the detection of the saccade.

For both adaptation and control exposure, the task comprised 144 trials, presented in 3 blocks of 48 trials, respectively referred to as exposure 1, exposure 2 and exposure 3. Between each block, subjects were allowed a 10 to 30 second rest.

The pre- and post-exposure saccadic tasks were identical to the exposure tasks except that in this case, the visual target could appear in either hemifield and was turned off at the detection of the saccade (no visual feedback). Each pre- and post-exposure task consisted in one block of 24 trials (12 for each side, randomly presented). Comparison between pre- and post-exposure saccadic tasks allowed determination of the adaptation after-effect (relative change of saccade amplitude in post-versus pre-exposure) and thus quantitative assessment of the SA behavioral efficiency.

1.2.3. Discrimination task

The exogenous attentional task (Fig. 1C) was performed before and after the exposure tasks (referred to as pre-exposure discrimination and post-exposure discrimination, respectively) and consisted in 4 blocks of 48 trials (192 in total). Subjects had to fixate a central LED which remained continuously on. A peripheral LED was flashed after a delay from 1000 to 2090 ms (uniformly randomized) at a randomly selected position among 4 possible locations (equal probability: 12 repetitions each) either in the left hemifield (-7° or -3° of eccentricity) or in the right hemifield (3° or 7° of eccentricity). Subjects were instructed to discriminate as fast as possible the hemifield of the target by using a two-button box in their right hand: they had to push the left button with their

index for a left target and the right button with their middle finger for a right target. The two-button box was in the subjects' right body space. The target LED turned off as soon as the answer was provided or after a limiting time of 600 ms. The trial ended 1300 ms after the target onset. Between each block, subjects were allowed a 10 to 30 seconds rest. The end of the entire task was signaled by the extinction of all LEDs. Trials in which a blink occurred within a 500 ms period before the target onset were aborted. Subjects were told to blink just after providing their answer.

1.3. Behavioral data Analyses

1.3.1. *Saccadic tasks*

Pre-processing. The eye movement data were analyzed off-line using custom software developed in Matlab (Math Works Inc., Natick, MA, USA). The beginning and end of each saccade were identified based on a velocity threshold of 30°/s. Saccadic amplitude was the difference between eye positions measured 50 ms before saccade onset detection and 50 ms after saccade offset detection. The gain was computed as the ratio of the saccadic amplitude and target retinal eccentricity (difference between target position and starting position of the saccade). The saccadic peak velocity was also extracted and divided by the amplitude of the saccade to obtain a normalized peak velocity. For the pre-exposure, the exposure and the post-exposure saccadic tasks, trials in which the saccadic gain was less than 0.5 or outside the range of ± 3 SD from the subject's mean gain computed in the same phase and hemifield, were discarded from further analysis. Trials with a blink or an anticipated saccade (falling within the -1000 ms pre-target to 100 ms post-target period) were also discarded, leaving on average 23.4 trials \pm 1.3 (SD by subject) per saccadic task (24 in total) and 135.4 trials \pm 6.5 (SD by subject) per exposure task (144 in total). The repartition of saccadic valid trials (after rejection of invalid saccades) was tested using a rmANOVA with the

side of the target appearance (left or right), the phase (pre and post-exposure) and the session (adaptation or control) as within-factors. No main effect of target side on the amount of valid trials was found ($F(1,11) = 47.8$; $P = 0.50$), nor any interaction between the side and the other factors (side x phase: $F(1,11) = 34.4$; $P = 0.57$; side x exposure: $F(1,11) = 1.32$; $P = 0.27$; side x phase x exposure: $F(1,11) = 9.371668.10^{-28}$; $P = 1$). Finally, to check for the repartition of valid trials in the exposure task, we performed a rmANOVA with the factor exposure (adaptation or control). Again, no main effect of the exposure was highlighted ($F(1,11) = 9231$; $P = 0.78$).

Statistical analysis. Since SA was critical to our hypothesis, we needed to ensure that subjects showed a significant decrease of saccade gain only after the adaptation exposure in the adapted left hemifield. Thus, for each individual, we performed a unilateral Student t-test comparing the saccade gain between the pre- and the post-exposure phases, separately for each exposure and for each hemifield of target appearance. The resulting 48 p-values were corrected for multiple comparison using the False Discovery Rate (FDR; Benjamini and Hochberg 1995) correction.

We computed the percentage of gain change achieved in each block relative to the final gain change (measured in exposure block 3), and then compared these percentage values between exposure 1 and 2 and between exposure 1 and 3 using an unilateral student test corrected using the FDR correction.

Finally, to rule out the hypothesis that SA exposure could result in a period of arousal, we used the peak velocity as a marker of arousal (Di Stasi et al. 2013). Therefore, we computed for each subject, each exposure, each phase, the mean normalized peak velocity. We performed a repeated measures ANOVA (rmANOVA) on normalized peak velocity (dependent variable) with the phase (pre and post-exposure) and the exposure condition (adaptation or control) as within-subjects factors.

1.3.2. *Discrimination task*

Pre-processing. Data of the discrimination phase were analyzed with the open-source software R (The R Core Team, 2013). Only trials with a correct response were considered. Trials with a reaction time (RT) outside the 200-600 ms time window after target onset or exceeding ± 3 SD from the subject's mean were also excluded, leaving on average 174.3 trials \pm 4.85 (SD by subject) per task (192 in total). The repartition of the amount of valid trials (dependent variable) was tested using a rmANOVA with the side of the target appearance (left or right), the phase (pre and post-exposure) and the session (adaptation or control) as within-factors. We found only a significant side effect ($F(1,11) = 6.31$; $P = 0.03$) consistent with the frequently observed hemifield imbalance of visuo-motor performance, but importantly for our behavioral analysis there was no interaction between the side and the other factors (side x phase: $F(1,11) = 0.20$; $P = 0.66$; side x exposure: $F(1,11) = 0.65$; $P = 0.44$; side x phase x exposure: $F(1,11) = 0.52$; $P = 0.48$).

Statistical analysis of RTs. A rmANOVA was performed on median RTs (dependent variable) with the side of the target appearance (left or right), the phase (pre and post-exposure) and the session (adaptation or control) as within-factors. Paired Student t-tests were used as post-Hoc analysis on the main effects revealed by the rmANOVA. Power analysis was performed through the G*Power software (Faul et al. 2007) with a total sample of 12, one group (within design), 16 repetitions, correlation among subjects of 0.5, and ϵ coefficient for non sphericity correction of 0.36 for the target position factor in the discrimination task.

1.4. Magnetoencephalography

1.4.1. *Data acquisition*

The MEG data were acquired with a 275-sensor axial gradiometer system (CTF Systems Inc., Port Coquitlam, Canada) with a continuous sampling rate of 600 Hz, a 0–150 Hz filter bandwidth, and first-order spatial gradient noise cancellation.

Head position relative to the gradiometer array was acquired continuously using coils positioned at three fiducial points: nasion, left and right pre-auricular points. Head position was checked before each block to ensure that head movements did not exceed 1 cm in comparison to the first block.

Anatomical head/brain images (either available beforehand or obtained using a 3T Siemens Magnetom whole-body scanner, Erlangen, Germany) were used for reconstruction of individual head shapes to create forward models for the source reconstruction procedures. The co-registration of the fiducial points was carried out using CTF's software (CTF Systems Inc., Port Coquitlam, Canada).

1.4.2. *Preprocessing and trials rejection*

Electrophysiological analyses concerned data collected during the pre- and post-exposure discrimination and saccadic tasks, as well as during the exposure blocks 1, 2, and 3. The aim of the study was to investigate lasting effects of SA on neuronal excitability by isolating persistent changes of GBA across trials. Therefore, we avoided the time windows during which other types of processing - such as the computation of post-saccadic error - could happen, and electrophysiological analyses were hence focused on the pre-target period in all the tasks.

First of all, trials already excluded at the behavioral pre-processing step were discarded from the electrophysiological analyses. Trials with head movements exceeding 1 cm (up to 1.3 cm for 2 subjects) were also discarded, as well as trials with a blink occurring in the 1000 ms period preceding presentation of the peripheral target. Data segments contaminated with muscular activity or sensor jumps were excluded semi-manually with a threshold of 2,500 and 10,000 femto-tesla respectively, using the ELAN software package for electrophysiological analysis (<http://elan.lyon.inserm.fr/>; Aguera et al. 2011). In total, 20 trials \pm 3 (SD) in the saccade tasks, 34.8 trials \pm 8.3 in each block of the exposure tasks and 163.7 trials \pm 12.4 in the discrimination tasks remained for the analysis. The amount of valid trials was not significantly different between adaptation and control conditions, neither in the saccade tasks ($\chi^2(33) = 11.6$, $p = 0.99$), nor in the exposure task ($\chi^2(55) = 64.4$, $p = 0.18$) and nor in the discrimination tasks ($\chi^2(33) = 25.4$, $p = 0.83$). Data were filtered with a high-pass filter at 0.01 Hz and with band-stop filters between 47-53 Hz, 97-103 Hz and 147-150 Hz. MEG data pre-processing and analyses were carried out using functions supplied by the fieldtrip toolbox (REF; <http://www.ru.nl/neuroimaging/fieldtrip>; Oostenveld et al. 2011).

1.4.3. *Sensor-Level Analyses*

Time-Frequency (TF) representations were calculated using Morlet Wavelet decomposition with a width of four cycles per wavelet ($m=7$) at center frequencies between 30 and 150 Hz, in steps of 1 Hz and 10 ms, and averaged across all trials of each condition (phases of discrimination task, phases of saccadic task, blocks of exposure task, and type of session: adaptation or control). Data extracted in the pre-exposure saccadic task were used as baseline data for the analyses of exposure 1, 2 and 3, as well as of the post-exposure saccadic task, whereas data in the pre-exposure discrimination

task were used as baseline for the analysis of the post-exposure discrimination task; in all cases, baseline time-window was defined as the 900 to 100 ms pre-target period to prevent any contamination of the baseline signal by blink- or target-related activity:

$$Baseline_{saccade} = \text{mean}(\text{Gamma power}_{saccade PRE [-900; -100]})$$

$$Baseline_{Exposure} = \text{mean}(\text{Gamma power}_{saccade PRE [-900; -100]})$$

$$Baseline_{Discrimination} = \text{mean}(\text{Gamma power}_{Discrimination PRE [-900; -100]})$$

Then we computed for each task of interest the change of gamma power relative to baseline, by dividing each TF point of each sensor by the corresponding mean baseline activity, according to the following expressions:

$$\% Adaptation or Control_{task of interest} = \frac{\text{Gamma power}_{task of interest} - Baseline}{Baseline}$$

The data were smoothed in the time domain (50 ms) and in the frequency domain (5 Hz). The sensor-level analysis performed on every time-frequency points allowed us to decipher the frequencies and time-windows for which the SA effect was the strongest. Then, we computed the difference between *% Adaptation* and *% Control*. For the statistical contrast, this difference was compared to zero using a nonparametric cluster-based permutation (CBP) analysis (Maris and Oostenveld 2007). This test first calculates paired t-tests between *% Adaptation* and *% Control* for each sensor at each TF points, which are then thresholded at a chosen p-value which sets the conservativeness of the test (reported as ‘cluster threshold’). We decided to set the cluster threshold to be as conservative as possible while obtaining comparable cluster size among the different tasks. Significant clusters are defined as sets of adjacent sensors showing a continuum of significant TF points. Subsequently, the procedure is repeated 1000 times on shuffled data in which the condition assignment (*% Adaptation* and *% Control*) within each individual is permuted randomly. On each

permutation, the maximum t-value is retained, yielding a distribution of 1000 t-values values. Finally, this distribution is used as a reference to determine whether the t-value of each cluster, as calculated on the real assignment of the conditions, is likely to come from the same probability distribution ($p\text{-value} > 0.05$) or rather differs significantly from this random perturbation probability distribution ($p\text{-value} < 0.05$).

The pre- and post-exposure saccadic task. To determine an effect of SA on GBA we computed the change of the GBA during the post-exposure saccadic task relative to baseline for the adaptation and control sessions (*% Adaptation Saccade* and *% Control Saccade*, as defined above). The difference between these values was then compared to zero with the same CBP analysis as described above, allowing to assess the specific impact of SA on GBA. As neutral outcome criterion, we used the same procedure to compare the raw GBA of the pre-exposure saccadic phase between the adaptation and the control sessions.

The saccadic exposure task. We proceeded identically for the exposure task, considering the three exposure blocks separately. The change of the GBA relative to the baseline was computed in exposure 1, 2 and 3 separately for the adaptation session (e.g. *% Adaptation Exposure 1*) and for the control session (e.g. *% Control Exposure 1*). For each exposure block, the difference between these values was then compared to zero with a CBP analysis, allowing to assess the specific impact of SA on GBA during each block of the exposure.

The discrimination task. We computed the change of GBA in post-exposure discrimination relative to baseline, separately for the adaptation session (*% Adaptation Discrimination*) and for the control session (*% Control Discrimination*). Again, the specific impact of SA was extracted by comparing the difference of the two relative changes to zero through a CBP analysis. As neutral outcome criterion,

we used the same procedure to compare the raw GBA of the pre-exposure discrimination of the adaptation and the control session.

Since our initial hypothesis was interested in the effect of SA on an attentional task, the CBP used to analyze the discrimination task implemented a two-tailed paired Student t-test. This revealed significant positive modulations (see Results section paragraph 2.2) which led us to look for positive modulations in the other tasks, using one-tailed tests.

In summary, we derived five main contrasts of interest, each of which being then submitted to a CBP analysis. We performed the permutations over a 800 ms period of interest, from 900 ms to 100 ms pre-target. The frequency range was set from 50 to 100 Hz.

$$\begin{aligned} \text{Saccade contrast:} & \quad \% \text{ Adaptation}_{\text{Saccade}} \quad \mathbf{VS} \quad \% \text{ Control}_{\text{Saccade}} \\ \text{Exposure contrasts:} & \quad \% \text{ Adaptation}_{\text{Exposure 1,2 or 3}} \quad \mathbf{VS} \quad \% \text{ Control}_{\text{Exposure 1,2 or 3}} \\ \text{Discrimination contrast:} & \quad \% \text{ Adaptation}_{\text{Discrimination}} \quad \mathbf{VS} \quad \% \text{ Control}_{\text{Discrimination}} \end{aligned}$$

1.4.4. *Source-level Analyses*

These analyses aimed at estimating the candidate brain regions driving the modulation of GBA disclosed by the sensor-level CBP analysis (see Results section paragraph 2.2). In these TF windows, we have used the frequency–domain adaptive spatial technique of dynamical imaging of coherent sources (DICS; Gross et al. 2001). First, data from the two entire sessions were concatenated, and cross-spectral density (CSD) matrix (from -900 to -100 ms relative to target onset, lambda 15%) were calculated using the multitaper method with a target frequency of 75 Hz ± 15 . For each subject, an anatomically realistic single-shell head model was generated based on individual head shapes (Nolte 2003). A grid with 0.5 cm resolution was normalized on a MNI template, and then morphed into the brain volume of each subject. Leadfields for all grid points

along with the CSD matrix were used to compute a common spatial filter allowing to estimate the spatial distribution of power for all TF windows of interest. Based on the most pronounced significant differences found at the sensor-level and the observation of the data, we decided to choose for all saccadic tasks (pre- and post-exposure, and the 3 exposure blocks) an a-priori time-window of 300 ms starting at -400 ms before target onset. Following the same types of observation of the data, time-windows of both discrimination pre-exposure (used as baseline) and discrimination post-exposure were selected as 900 to 100 ms pre-target. The frequency bands were chosen to encompass the most pronounced differences observed at the sensor level across all tasks, leading to a common frequency band of 75 ± 15 Hz.

Then, following the same rational as for the sensor-level analyses, the GBA differences between % *Adaptation* and % *Control* were computed and tested against zero using a CBP analysis.

2. RESULTS

2.1. Behavioral analyses

2.1.1. Pre- and post-exposure saccadic tasks

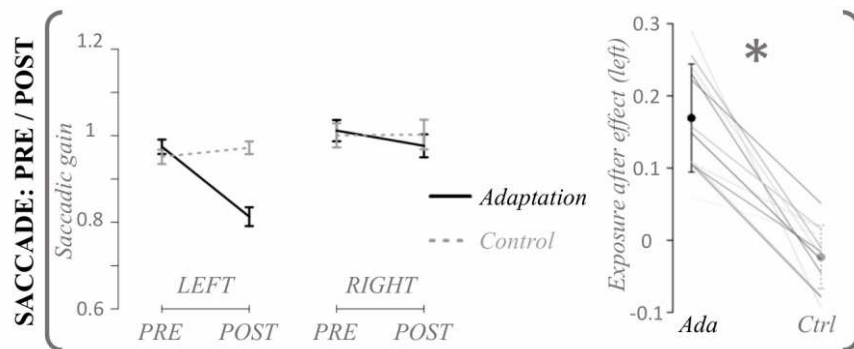


Figure 2: Pre- and Post-exposure saccadic task showing the efficiency of the leftward saccadic adaptation. **Left:** Group mean (+/- SEM) of saccadic gain. **Right:** Individual data of percent gain change between the pre- and the post-

exposure tasks. Solid black and dotted grey for group mean (\pm SD) of the adaptation and the control exposure, respectively. Gray lines stand for individual values.

The mean saccadic gain in pre- and post-exposure, as well as the individual and mean adaptation after-effect, are illustrated in Figure 2. Eleven subjects showed in the adaptation session a significant decrease of the saccadic gain for target presented in the left hemifield in the post-exposure as compared to the pre-exposure, with corrected p-values < 0.05 (type I error threshold), the twelfth subject had an effect approaching significance with a p-value of 0.053. The twelve results all achieved a power larger than 98% and a large effect size (>0.9), we thus considered that all subjects demonstrated a significant after-effect due to SA. Moreover, no significant modulation of saccadic gain was highlighted, neither for responses toward both hemifields in the control session nor for responses toward the right hemifield (un-adapted) in the adaptation session.

Regarding the normalized peak velocity, we found no effect of the exposure ($F(1,11) = 2.03$; $P = 0.18$), nor an effect of the phase ($F(1,11) = 0.26$; $P = 0.62$), and nor an interaction between the exposure condition and the phase ($F(1,11) = 1.17$; $P = 0.3$).

2.1.2. *Exposure saccadic task*

As shown in Figure 3, most of the saccadic gain change reached at the end of adaptation exposure was achieved during exposure 1 (on average $47.9 \pm 25\%$), then during exposure 2 ($33.4 \pm 16.9\%$) and exposure 3 ($18.6 \pm 19.9\%$). The difference between the percentage of adaptation achieved during exposure 1 and exposure 2 is not significant ($t_{(11)} = 1.33$; $P = 0.11$). The percentage achieved in exposure 1 is significantly larger than that achieved in exposure 3 (Cohen's $d = 1.28$; $t_{(11)} = 2.42$; $P = 0.017$; corrected to 0.034 with the FDR correction; achieved power = 0.97).

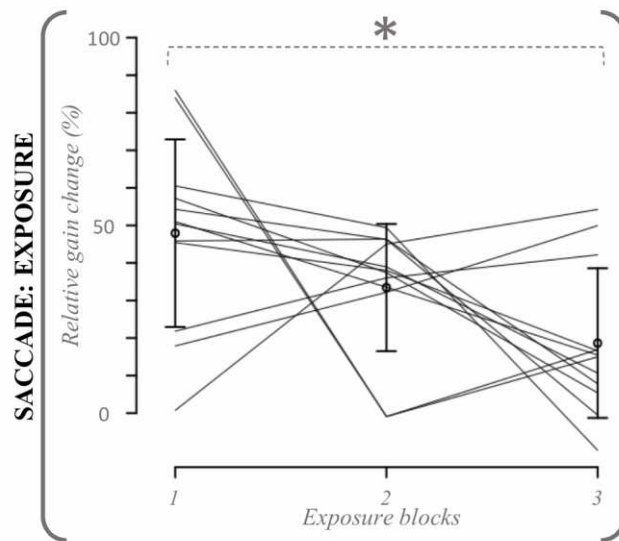


Figure 3: *Percentage of saccadic adaptation during exposure. Percent gain change (relative to total gain change reached at exposure 3) for each exposure block: individual data and group mean are plotted as black lines and black points (+/- SD), respectively.*

2.1.3. Discrimination task

The performance in the discrimination task was evaluated by computing the median reaction time of subjects' discrimination responses. The rmANOVA revealed a significant main effect of phase (pre- vs post-exposure, partial $\eta^2 = 0.49$; $F_{(1,11)} = 10.6$; $P = 0.008$; achieved power = 0.99). As shown in Figure 4, post-hoc unilateral paired Student t-tests indicated that subjects were faster after the exposure task (either adaptation or control) in comparison to before exposure ($t_{(11)} = 3.19$; $P=0.009$). However, this phase effect did not significantly interact with the type of exposure, nor with the target hemifield. This indicates that the tendency which can be seen in Figure 4 (compare left and right panels) does not reach significance, contrary to our predictions. In conclusion, these behavioral data disclosed a general improvement of performance after exposure, but no specific effect of adaptation on discrimination performance could be statistically established.

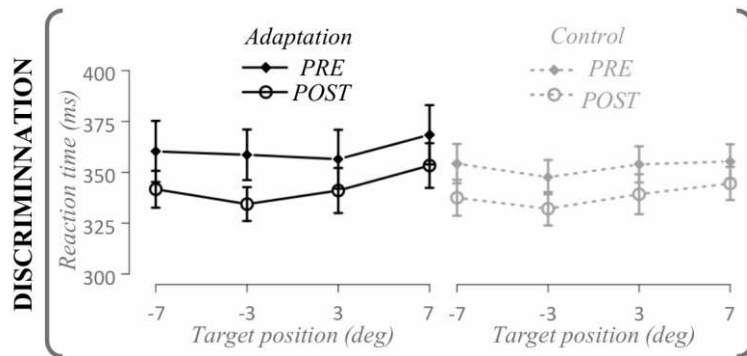


Figure 4: Pre- and Post-exposure behavioral results of the reaction times in the discrimination task. Group mean (\pm SEM) of median reaction times (ms) in the adaptation session (left panel) and in the control session (right panel). A general decrease between the pre and the post-exposure phases is observed but is not specific to the exposure conditions.

2.2. Sensor-level analyses

Neutral outcome criteria. We first verified that the GBA used as baseline in our analyses presented below did not differ significantly between, on the one hand, the pre-exposure saccadic task of the

adaptation and the control session and, on the other hand, the pre-exposure discrimination task of the adaptation and the control session. None of these tests did disclose any significant result, allowing us to use these periods to compute baseline GBA.

Pre- and post-exposure saccadic task (Fig. 5 top panels). Testing for the saccadic task contrast, the CBP test revealed a trend to significance of the difference between the two exposure types. This trend was most pronounced from 400 ms to 100 ms before the target and from 50 to 100 Hz over two localizations: one on a broad right area of sensors and the second on a left posterior area, with a cluster threshold of 0.05 and p-value of 0.09.

Exposure task. Using the CBP test separately for the three exposure blocks as defined in Methods revealed no significant difference between the adaptation and the control sessions for any of these contrasts (exposure 1, exposure 2 or exposure 3) at the sensor level.

Discrimination task (Fig. 5 bottom panels). Testing for the discrimination contrast, the CBP test revealed a significant difference between the two exposure types. This difference was most pronounced over two localizations: one on right anterior sensors and the second on a left posterior area. The difference was sustained in time (during the entire period of interest from -900 to -100 msec) at both localizations and was from 70 to 100 Hz for the right anterior sensors and from 60 to 90 Hz for the left posterior sensors. The cluster threshold was 0.005 and a p-value of 0.001.

To summarize, we found differences of GBA between adaptation and control conditions that tended to or was highly significant, respectively for the saccade and discrimination contrasts. Note that in left hemisphere, the clusters overlap between the two tasks, and in the right hemisphere some overlap is also observed.

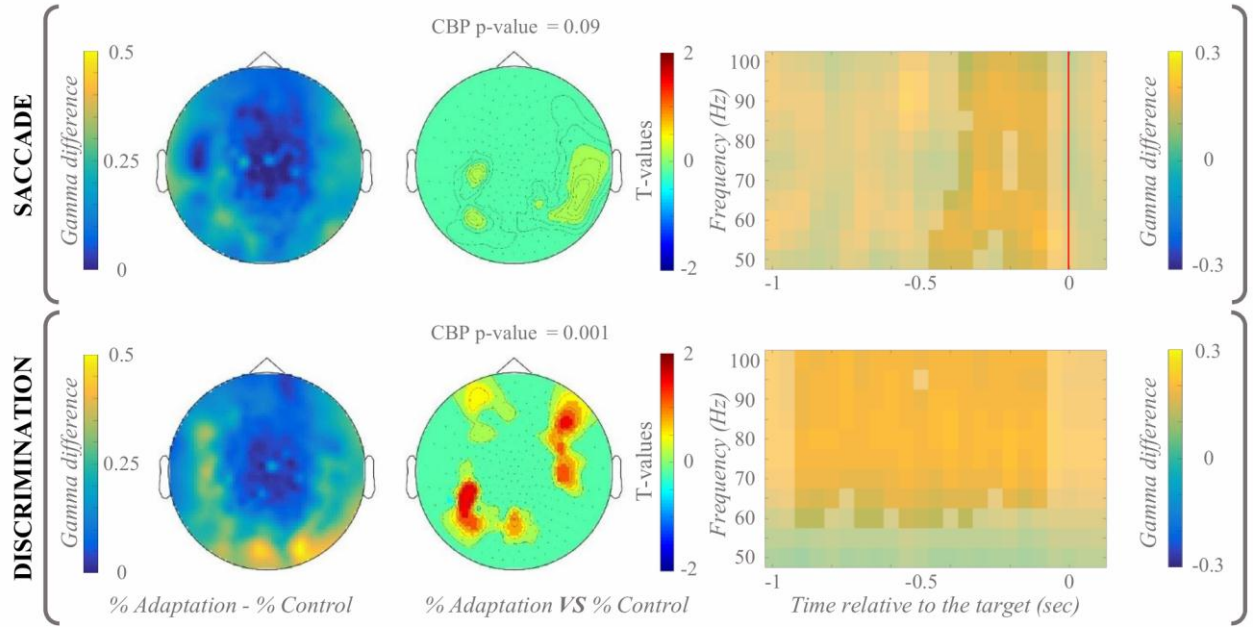


Figure 5: *Gamma difference between adaptation and control evidencing the specific increasing effect of the exposure to SA. Left: Topographies of group grand average power (60-90 Hz) from 900 ms to 100 ms pre-target. Middle: T-values topographies of the CBP analysis masked at $P=0.1$ for the saccade task and at $P=0.05$ for the discrimination task. Right: Time frequency plots of the average power the gamma difference across significant clusters.*

2.3.Source-Level Analyses

After selecting the time and frequencies of interest from the CBP analysis at the sensor level (see Results section paragraph 2.2), the cluster-based permutation tests revealed a difference of GBA modulation between adaptation and control conditions, as detailed below. The cortical regions highlighting more than 10 significant voxels are listed in Table 1 for both the pre- and post-exposure saccadic (referred as *Saccade*) task and the discrimination task (referred as *Discrimination*).

Pre- and post-exposure saccadic task. We found a difference with a cluster threshold of 0.02 and a p-value of 0.056 (Fig. 6 upper left panel). Although this p-value did not reach the classical statistical

threshold, it is very close to significance and we consider this result as noteworthy because (1) the small number of trials in this task likely contributed to this failure to reach significance (maybe explaining also the large size of the cluster), (2) a similar pattern of GBA increase in the discrimination phase clearly reached statistical significance ($p\text{-value} = 0.001$) with only one additional subject showing the effect (Fig. 6 lower right panel: 11 subjects) as compared to the 10 subjects for the discussed GBA change in the adaptation phase (Fig. 6 lower right panel), (3) a significant correlation was found between the SA gain change and the GBA activity during adaptation exposure in the right parietal cortex (Supplementary Results).

Discrimination task. For the discrimination contrast, we found a significant difference with a cluster threshold of 0.008 and a $p\text{-value}$ of 0.001 (Fig. 6, lower left panel).

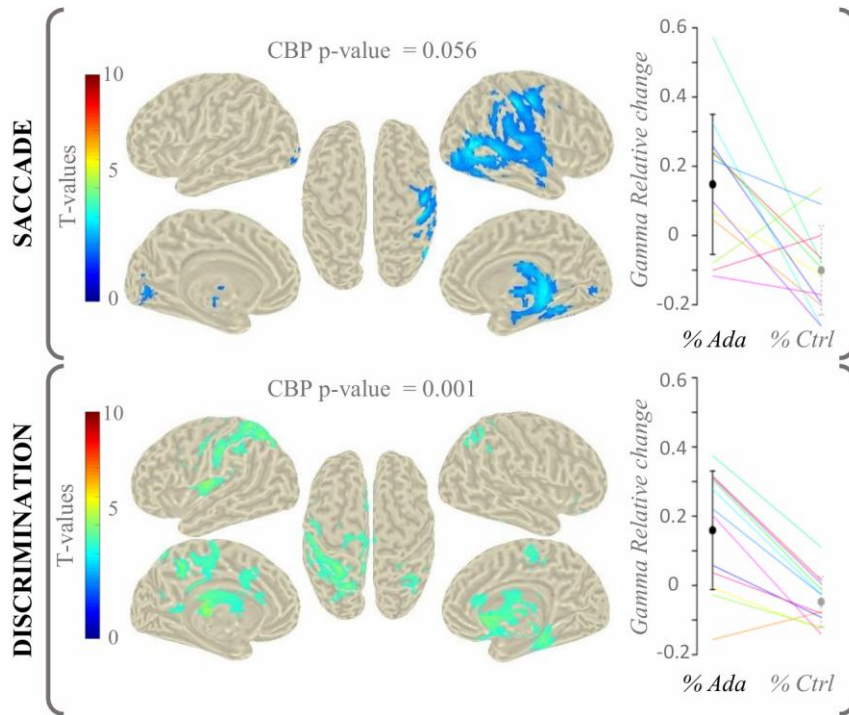


Figure 6: Source reconstruction of the positive gamma power increase in the saccadic task (top) and the discrimination task (bottom). **Left:** T-values distributions of the adaptation versus control contrast, masked at $P=0.05$, are displayed on surface cortical maps. **Right:** Average gamma power (\pm SD) change across significant voxels for the adaptation session (solid black) and for the control session (dotted grey). Individual data are represented by colored lines.

Table 1: Cortical and subcortical regions found from the CBP analysis at the source level.

Region	Left hemisphere	Right Hemisphere
Angular	<i>Discrimination</i>	
Calcarine	<i>Saccade</i>	
Caudate	<i>Discrimination</i>	<i>Discrimination</i>
Cingulum	<i>Discrimination</i>	
Fusiform		<i>Saccade / Discrimination</i>
Heschl		<i>Saccade</i>
Hippocampus		<i>Saccade / Discrimination</i>
Insula	<i>Discrimination</i>	<i>Saccade</i>
Lingual	<i>Saccade</i>	
Occipital Inferior		<i>Saccade</i>
Occipital Middle	<i>Saccade</i>	<i>Saccade</i>
Parahippocampal		<i>Saccade / Discrimination</i>
Paracentral Lobule	<i>Discrimination</i>	<i>Discrimination</i>
Parietal Inferior	<i>Discrimination</i>	<i>Saccade / Discrimination</i>
Parietal Superior		<i>Discrimination</i>
Postcentral		<i>Saccade / Discrimination</i>
Precentral		<i>Saccade / Discrimination</i>
Precuneus		<i>Discrimination</i>
Putamen		<i>Saccade</i>
Rolandic Operculum		<i>Saccade / Discrimination</i>
Supramarginal		<i>Saccade</i>
Temporal Inferior		<i>Saccade</i>
Temporal Middle		<i>Saccade</i>
Temporal Superior		<i>Saccade</i>
Thalamus	<i>Discrimination</i>	<i>Saccade / Discrimination</i>

3. DISCUSSION

Gamma band activity (GBA) has been previously shown to increase in relation to various perceptual, motor and cognitive processes (see Introduction). Here, we questioned the link between GBA and these processes combined together, thanks to a design testing the effect of oculomotor plasticity on exogenous attention. Furthermore, this study is the first to report whole-brain electrophysiological signal changes in relation to saccadic adaptation (SA). Based on within-subjects comparisons between saccadic adaptation and control exposures, our results highlighted a sustained SA-specific increase of the GBA. More precisely, during the post-exposure saccadic task, a trend of GBA increase was disclosed in widespread areas of the right hemisphere including the inferior parietal lobe, the superior temporal lobe, the supramarginal gyrus region, the insula, and the sensorimotor cortex (Table 1). In addition, during the post-exposure attentional task, a strong GBA increase was found in both hemispheres.

One major finding is that GBA can be entrained by SA, a well-established model of sensorimotor plasticity. SA requires a continuous change in the brain's functional architecture to encode the new relationship binding the sensory vector, representing the position of the target from the current gaze position, and the motor vector sent to the extraocular muscles to accurately shift gaze position towards this target. The parietal cortex and the supramarginal regions at the temporo-parietal junction were found to be modulated by SA. These findings provide further support for an involvement of the parietal cortex and of the temporo-parietal junction in SA, complementing previous fMRI and TMS data in humans (Gerardin et al. 2012; Panouillères et al. 2014; Pélisson et al. 2018). They are also consistent with recent electrophysiological recordings in monkey area LIP (Zhou et al. 2016). As will be detailed below, we suggest that the increase of GBA that we disclose in the cerebral cortex, is a signature of the error processing subtended by the cerebellum.

Note however that an additional involvement of GBA directly underlying the plastic change of saccadic commands during SA cannot be excluded. In addition, as the other neurophysiological studies of SA in humans or monkey have neglected the cerebral cortex and rather focused on the brainstem-cerebellum circuits (see for reviews: Iwamoto and Kaku 2010; Pélisson et al. 2010; Prsa and Thier 2011), the available evidence in the literature is too limited to allow us to fully understand the large extent of the cortical and sub-cortical network where we found an increase of GBA. Nevertheless, regarding the parietal cortex, the SA-induced GBA increase could correspond to a more general role in motor plasticity, as gamma activity during hand movement execution has been shown to be enhanced after visuo-manual learning, in sensors above the right parietal lobe (Perfetti et al. 2011). The involvement of GBA in numerous forms of functional plasticity is supported by its proposed link with cellular plasticity mechanisms. Actually, GBA represents a precise temporal framework for synaptic plasticity in terms of gain modulation of synaptic weight (Bosman et al. 2014; Traub et al. 1998). We thus propose that the GBA increase in the regions at the crossroad of somatosensory, temporal and parietal cortices reported here subtends the updating of visuo-motor maps. Such SA-related updating of visuomotor maps has been predicted based on behavioral data of adaptation transfer to visually-guided motor tasks and to visual localization tasks (reviewed in Zimmermann and Lappe 2016). The information for the updating could be provided via the cerebello-thalamo-cortical pathway, as the cerebellum is suggested by the literature to compute an error signal between the predicted and actual motor consequences (Peterburs and Desmond 2016). The involvement of the parietal cortex, conjunctly with the cerebellum, in visuo-motor plasticity has also been studied thanks to the Prismatic Adaptation (PA) paradigm. In this case, sensorimotor adaptation of arm reaching movement is induced thanks to a visual shift elicited by prismatic goggles. In the model proposed by Pisella et al. (2005), the progressive modification of the arm

movement is thought to rely on cerebello-cortical interactions, whereby the cerebellum inhibits the posterior parietal cortex (PPC), a cortical involvement which could account for the known effects of PA on spatial cognition (Striemer and Danckert 2007; Reed and Dassonville 2014; Jacquin-Courtois et al. 2013). Although much less investigated than PA, SA might also involve cerebello-thalamo-cortical interactions. Indeed, SA heavily relies on the cerebellum (e.g. Prsa and Thier 2011; Straube et al. 2001; Desmurget et al. 1998; Golla et al. 2007; Panouillères et al., 2012; Panouillères et al., 2015). Moreover, Prevosto et al. (2010) reported that, in monkeys, the cerebellum projects via the thalamus to the parietal cortex and especially to the LIP, known to be involved in eye movement and visuospatial attention (Colby et al. 1995). In addition, clinical observations suggest that SA involves the cerebello-thalamo-cortical pathway (Gaymard et al. 2001; Zimmermann et al. 2015). Finally, SA affects visual cognition (Hernandez et al. 2008; Cotti et al. 2009; Zimmerman and Lappe 2010; Habchi et al. 2015; Khan et al. 2010) and involves the parietal and temporo-parietal cortices (Gerardin et al. 2012; Panouillères et al. 2014). The present results support this hypothesis of cerebello-cortical interactions subtending SA, and further suggest that the updating of spatial representations in the parietal cortex following SA is mediated through GBA changes.

The presently reported involvement of the temporal cortex and of the sensorimotor cortex was less expected. However, note that the contribution of motion sensitive areas of the temporal cortex (MT/V5) is consistent with the fMRI finding of an activation related to the adaptation of reactive saccades (Gerardin et al. 2012). Concerning the sensorimotor cortex, an intriguing hypothesis is that, although extraocular proprioceptive afferents seem not necessary for SA in the monkey (Lewis et al. 2001), SA modifies the eye position sense derived from extraocular proprioception. Indeed, studies in the monkey and in humans have suggested that eye proprioceptive signals are processed

bilaterally in an area of the sensorimotor cortex (Balslev et al. 2011; Wang et al. 2007). What are the relative weights of proprioceptive and of efference copy signals in the SA-related changes of eye position sense, and to what extent their cortical neural substrates overlap, remain to be determined.

Finally, the involvement of the insula in the right hemisphere during the post-exposure saccadic task and in the left hemisphere during the post-exposure discrimination task echoes a fMRI study (Blurton et al. 2012) which reported a bilateral activation of the insula during SA. These authors suggested that such insula activation disclosed by contrasting the SA exposure phase to the pre-exposure phase was related to saccade inaccuracy.

The initial objective of the present study was to decipher the neural substrates of the coupling between adaptation of reactive saccades and orientation of exogenous attention. Such coupling is supported by converging evidence (McFadden et al. 2002; Khan et al. 2010; Gerardin et al. 2015; Habchi et al. 2015). Unfortunately, although using an identical design to Habchi et al. (2015), we failed to reproduce their finding of a significant decrease of discrimination reaction times specifically after adaptation of leftward reactive saccades. Note however that these two experiments differ in the stimuli used: the contrast of their targets (grey circles presented on the grey background of a computer screen) was 50% whereas in the present study, due to MEG environment constraints, targets (red LEDs on a black background) reached a contrast of 100%. Given that attention increases the sensitivity to contrast (Carrasco et al. 2000), we interpret our negative finding as related to the too high contrast of our stimuli which did not provide optimal condition for attentional performances to be boosted by SA. The unspecific decrease of RT after both adaptation and control exposures suggests a learning effect between pre- and post-exposure, possibly further masking any residual effect of SA on attention. Nonetheless, it is still possible that

some specific effect of SA on attention can be reflected in the neural dynamics. Indeed, previous studies of PA reported significant changes of metabolic or electrophysiological markers of cognitive functions without any behavioral evidence (Crottaz-Herbette et al. 2014; Martin-Arevalo et al. 2016). The large extent of the network showing a specific GBA increase after SA could suggest that the latter led to an increase in arousal. However, we found no evidence for an increase after SA of saccade peak velocity, as a sensitive marker of arousal (Di Stasi et al. 2013). Thus, changes of arousal are unlikely to account for the observed GBA modulations.

Furthermore, GBA increased, preferentially in the left hemisphere and in sensorimotor areas, during the subsequent discrimination task. Two explanations can be provided for this lateralization in the left hemisphere: either it resulted from the displacement of the source of GBA increase present in the right hemisphere during adaptation exposure or was already present during the SA exposure but could not be established statistically. In the frame of this latter alternative, we suggest that this activity (ipsilateral to the saccade) is related to the SA-inducing, intra-saccadic target jump toward the right hemifield, providing a rightward bias of the saccade aiming error. The resurgence of the GBA in the subsequent discrimination task could be the result of a retention of such a rightward bias introduced progressively during the adaptation procedure. We further suggest that this activity could account for the distortion of space demonstrated by previous behavioral studies. Indeed, Zimmermann and Lappe (2009) showed that SA induces a shift of the perceived localization of objects flashed before the saccade, and Zimmerman and Lappe (2010) demonstrated that this SA-related visual mislocalization occurs even when saccades were not executed, suggesting that spatial visual representations are shaped by oculomotor planning (Zimmermann and Lappe 2016). A possible common explanation of the effect of SA on localization (Zimmerman and Lappe 2010) and on attention (Habchi et al. 2015) is a SA-induced compression of represented

visual space (in case of backward adaptation) that would shift the representation of visual stimuli toward the center of gaze. Consequently, when subjects have to localize (Zimmermann and Lappe's) or simply detect (current study and Habchi et al.'s) such stimuli with no eye movement allowed, they would both underestimate the targets eccentricity and detect them with a faster reaction time. Further studies are required to fully address our hypothesis on the nature of GBA increase in the left hemisphere. For example, eliciting forward adaptation of leftward saccades should, following this rationale, elicit a GBA increase observed in sensorimotor cortex of the right hemisphere (related to the leftward bias of saccade aiming error), and in the right superior parietal lobule (related to the leftward saccadic vector).

Finally, we think that other cognitive processes sharing the same substrates as SA could benefit from this GBA increase. Indeed, it has been extensively demonstrated that increased behavioral performances are related to both post-stimulus induced-GBA (Fries et al. 2001) and pre-stimulus ongoing GBA (e.g. Hoogenboom et al. 2010). Also, GBA has been causally related to increase in performance in a neurofeedback study showing a subsequent beneficial effect of the GBA increase on perceptual performances (Salari et al. 2014).

To conclude, by conducting the first study in humans of the neurophysiology of oculomotor plasticity, we highlighted that GBA can be entrained in a large cortical network. This GBA modulation could be beneficial to other overlapping cognitive processes, opening new perspectives of rehabilitation of different cognitive impairments such as neglect.

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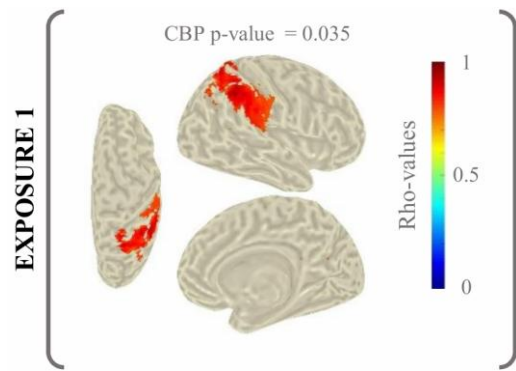
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1. SUPPLEMENTARY METHOD

Correlation between SA behavior and GBA. On the one hand, to quantify SA behavior, the amount of saccadic adaptation during the three saccadic exposure blocks was first computed for each subject as the mean saccadic gain change between each exposure block and the pre-exposure phase, separately in adaptation and in control sessions. The relative gain change in the control session was then subtracted from the relative gain change in the adaptation session. On the other hand, to extract the GBA change specifically related to SA, we computed, again separately for each subject and exposure block, the difference of GBA power between the *% Adaptation Exposure* and *% Control Exposure* (frequency range: 75 ± 15 Hz, time window: from 400 ms to 100 ms pre-target). Finally, the Spearman correlations between these two variables (SA behavior and specific GBA change) were calculated at the source level and their significance assessed using a cluster-based permutation analysis.

2. SUPPLEMENTARY RESULT

Correlation between SA behavior and GBA. We found that the GBA during exposure 1 of the adaptation (during which nearly 50% of the adaptation is achieved, Fig. 3) significantly correlated with the amount of SA. Namely, the more saccadic gain change, the more gamma power as compared to the pre-exposure saccadic task. At the source level, we found a cluster with a cluster threshold of 0.001 and a p-value of 0.035. This cluster was centered on the right parietal lobe (see Supplementary Fig. 1).



Supplementary Figure 1: Correlation across subjects between relative gain change and gamma band power relative change during Exposure 1. Rho-values distributions, masked at $P=0.05$, are displayed on surface cortical maps.

These results are considered as exploratory and should be treated with caution as the rho values reported here are likely inflated given the group size (Yarkoni, 2009). Given this caveat, we found interesting to report that the parietal cortex seems to be activated during exposure to saccadic adaptation.

SUPPLEMENTARY REFERENCES

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